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EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/668,778	BALINT ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *63,64,66 and 68-74* is/are pending in the application.

4a) Of the above claim(s) *64 and 68-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63, 66, and 71-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed May 4, 2007 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

Status of the Claims

3. Claims 63, 64 and 66-74 were pending. Applicants canceled claim 67 and amended claims 63, 64, 66, and 71. Therefore, claims 63, 64, 66, 68-74 are currently pending. Claims 64 and 68-70 are drawn to non-elected species and/or inventions and thus these claims remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), there being no allowable generic claim. Therefore, claims 63, 66, and 71-74 are examined on the merits.

Priority

4. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 1290 and/or 119(e) as follows:

This application is a CON of 09/526,106 03/15/2000 ('106), which claims benefit of 60/175,968 filed 01/13/2000 ('968) and claims benefit of 60/135,926 filed on 05/25/1999 ('926) and claims benefit of 60/124,339 filed on 03/15/1999 ('339). However, one or more of the

applications stated above fail to provide adequate support under 35 U.S.C. § 112, first paragraph for the claimed invention as follows:

> (A) For ***claims 63, 66, 67 and 71-74***, none of the applications provide support for the current genus of fragment complementation systems wherein "said first and second break-point termini are within 10 amino acids in either direction from a junction between 2 amino acid residues, wherein said 2 amino acid residues are within a solvent exposed loop between elements of secondary structure" (e.g., see New Matter Rejection below). In addition, Applicants are not in possession of fragments "at least" 25 amino acids long (e.g., see New Matter Rejection below).
> (B) For ***claims 68-70 and 72-74***, the '339 application fails to provide support for peptides segments that "enhance" functional reconstitution including HSE, EKR, QGN, DGR, GRR, and GNS.
> (C) For ***claims 68-70 and 72-74***, the '926 application fails to provide support for peptides segments that "enhance" functional reconstitution including HSE, EKR, QGN, DGR, GRR, and GNS.

If applicant believes this assessment is in error, applicant must disclose where in the specification support for these limitations can be found. See MPEP § 714.02. Therefore the filing date of the instant application is deemed to be its actual filing date, **September 22, 2003**.

5. Applicant states that this application is a continuation or divisional application of the prior-filed application (see above). A continuation or divisional application cannot include new matter. Applicant is required to change the relationship (continuation or divisional application) to continuation-in-part because this application contains the following matter not disclosed in the prior-filed application: See New Matter rejection below.

Response

6. Applicant's arguments directed to the above denial of 35 U.S.C. §§ 119(e) and120 priority were considered but deemed non-persuasive for the following reasons"

[1] Applicants argue, "[w]ith regard to the genus of fragment complementation systems comprising a first Class A β-lactamase protein break-point as presently recited in independent claim 63, Applicants direct the Examiner's attention to the support identified in Section II above, and to Section V regarding the New Matter rejections below" (e.g., see 5/4/07 Response, pages 9-10, especially, page 10, paragraph 3).

[1] Section V was addressed in response to the New Matter rejection below. Section II above also examines paragraph [0028] in addition to paragraph [0042] mention in the Section V but, again, this section fails to provide support for the currently claimed genus for essentially the same reasons set forth in the new matter rejection below.

[2] Applicants argue that they have "incorporated a limitation in claim 63 that the fragments are at least 25 amino acids in length" (e.g., see 5/4/07 Response, paragraph bridging pages 8 and 9).

[2] This issue was addressed in response to the new matter rejection below.

[3] Applicants argue, "Claim 66 is amended to include teh sequence from figure 2 ... with the exception that the number of the amino acids in figure 2 takes into account that the first 25 amino acids (not shown in the figure) represent a signal peptide sequence" (e.g., see 5/4/07 Response, page 9, first full paragraph).

[3] This issue was also addressed in response to the new matter rejection below.

Withdrawn Objections/Rejections

7. The 35 U.S.C. § 112, second paragraph rejection denoted "A" is withdrawn in view of Applicants' arguments and amendments to claim 63. The new matter rejection is withdrawn in

part in view of Applicants' cancellation of claim 67. The Wehrman et al. rejection is withdrawn in part in view of Applicants' cancellation of claim 67. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claims Rejections - 35 U.S.C. § 112, first paragraph

8. Claims 63, 66, 67 and 71-74 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed had possession of the claimed invention. This is a new matter rejection.

A. Claim 63 was amended in the 10/25/06 and 5/4/07 responses. However, the Examiner cannot find support for these amendments. Specifically, the specification does not provide support for "wherein said first and second break-point termini are within 10 amino acids in either direction from a junction between 2 amino acid residues, wherein said 2 amino acid residues are within a solvent exposed loop between elements of secondary structure." The specification at page 16, lines 27-28 reads, "the actual break-point could be within ten amino acid residues in either direction from an identified functional contiguous break-point junction." However, this statement refers to lines immediately above it (i.e., on the same page), which indicates that the ONLY "identified functional contiguous break-point junction" is E197/L198 or perhaps the broad 195-202 positions (e.g., see page 16, lines 10-15, "An exposed loop was identified by this method between two α-helixed of E. coli TEM-1 β-lactamase (approximately Thr195 to Ala202,

between helixes 7 and 8) within which the chain could be broken to produce fragment which could only complement for activity when fused to fos and jun helixes. Representative fragments with contiguous break point termini at Glu197 and Leu198 were designated α197 (N-terminal fragment) and ω198 (C-terminal fragment), and subsequently shown to produce selectable activity." Thus, it would appear that only one loop (i.e., Thr195 to Ala202) was identified, not all loops as currently claimed. In addition, the specification does not provide support for the currently claimed "at least 25 amino acids in length" limitation. The specification at page 16, lines 4 and 5 reads, "Fragments of less than 25 amino acids were considered non-viable,:" which is not equivalent to saying every sequence greater than 25 amino acids will work, which has no upper limit (e.g., see *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976) (wherein the court held "at least 35%" did not meet the description requirement because the phrase "at least" had no upper limit)).

Response

9. Applicant's arguments directed to the above New Matter rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "[t]he E197/L198 break-point is only a single example of possible break-points that can be used with the invention, and merely illustrates the success of the method

of searching the fragment space of a marker protein to identify suitable fragment pairs. The method of searching the fragment space includes introducing break-points into solvent exposed or flexible loops as described in paragraph [0037] of the Pre=Grant Pub. [of the present application] and at page 13, lines 16-19, of the '106 application ... Therefore ...the passage cited in paragraph [0042] ... do refer to the general method as disclosed in paragraph [0037]" (e.g., see 5/4/07 Response, pages 11 and 12, especially page 12, paragraph 1).

[1] Even if, *assuming arguendo*, paragraph [0042] does refer back to paragraph [0037] it still does not provide support for the currently claimed limitations as set forth in the rejection above. Paragraph [0037] only sets forth a general strategy for screening. It does not provide support for the ultimate fruits of this screening method (e.g., see *University of Rochester v. G. D. Searle & Co.*, 358 F.3d 916 (Fed. Cir. 2004) (wherein the CAFC struck down a similar "reach through" claim drawn to the administration of a selective Cox-2 inhibitor that Rochester had not yet discovered using their screening assay). Here, Applicants state, "an exhaustive search of the fragment space of most enzymes could be conducted with libraries of a manageable size. [For example,] [a]n exposed loop was identified by this method between two α-helixes of E.coli TEM-1 β-lactamase (approximately Thr195 to Ala202, between helixes 7 and 8)" (e.g., see 5/4/07 Response, page 16, paragraph 1). Thus, according to Applicants, an "exhaustive search" using the claimed method only identified "one" viable fragment pair, not the currently claimed genus of any pair with first and second break-point termini within 10 amino acids in either direction from a junction between 2 amino acid residues, wherein said 2 amino acid residues are within a solvent exposed loop between elements of secondary structure (e.g., see claim 63). Note also that this claim language reads on break points in different loops (i.e., the first break-

point in loop 1 and the second break-point in loop2), which Applicants' are clearly not in possession of because the specification only discloses breaking the lactamase into two pieces.

[2] Applicants argue, "further support ... can be found in Example 55 ... and the passage from the bottom of page 40 to the top of page 41 along with Table 5 in the '106 application" (e.g., see 5/4/07 Response, page 12).

[2] The Examiner respectfully disagrees. Applicants' quotation was taken out of context. The paragraph bridging pages 50 and 51, for example, was meant to teach the use of "break-point disulfides", which is not commensurate in scope with the claims (e.g., see paragraph bridging pages 40 and 41, "The ability of the break-point disulfide to enhance activation of TEM-1 α197/ω198 fragment complementation, suggests that break-point disulfide might be able to activate many enzyme fragment pairs which produce weak or no selectable activity with a heterologous interaction alone ... formation of a disulfide across the break-point should restore the integrity of the backbone, and should thereby help stabilize the active site of the complex. This idea [i.e., the idea of using break-point disulfides] was tested by screening nine additional pairs of TEM-1 β-lactamase fragments"). Table 5 confirms this and further serves to highlight the deficiencies with Applicants' arguments. For example, N52/S53, E63/E64, L91/G92, Q99/N100, and H158/V159 showed no activity (e.g., see Table 5). Thus, this passage does not support a first and second break-point termini within 10 amino acids in either direction from a junction between 2 amino acid residues, wherein said 2 amino acid residues are within a solvent exposed loop" because, as Applicants' own data shows, many of these loops do not result in viable reconstitution. For example, figure 3 shows an inter-domain loop at R61-R65 but Table 5, entry 2 makes it clear that the E63/E64 break point within this loop does not work. The same

holds true for N52/S53, L91/G92, Q99/N100, and H158/V159. Furthermore, even if, assuming arguendo, all of these junctions did show activity (which is not the case), it still wouldn't be representative of the currently claimed genus. All of the entries are adjacent break-points, which the claims are not limited to. Furthermore, none of the entries shows breaks in different loops (e.g., R61 and W229 leaving "three" fragments including N-terminus, C-terminus and the intervening R51 to W229 fragment), which also falls within the scope of Applicants' broad claims. Applicants' provide no examples or guidance with regard to reconstituting enzymes that have been broken into three fragments.

[3] Applicants argue, "With regard to the Examiner's allegation that the Applicants were not in possession of fragments less than 25 amino acids in length ... In an effort to expedite prosecution of the application ... Applicants have amended claim 63 to introduce a limitation that the class A β-lactamase fragments are at least 25 amino acids in length" (e.g., see 5/4/07 Response, pages 12 and 13).

[3] Applicants new limitation places no upper limit on the size of the amino acid length. Therefore, Applicants are not in possession of this new "at least" term either (see newly amended rejection above).

[4] Applicants argue, "With regard to the junctions set forth in claim 67, which are herby incorporated into claim 66 as currently amended ... [these] junctions have been renumbered to be consistent with the text of the specification and with the enumeration as shown in Figure 2. Support for the break-points can be found throughout the specification, in particular, in Figure 2 paragraph [0042] ... The break-points as previously numbered, prior to entry of this amendment, were enumerated as shown in SEQ ID NO:2. Although this sequence is identical to that shown

in Figure 2, the numbering is different. The numbering of the amino acid residues as shown in Figure 2begins with the histidine as residue 25. This numbering reflects the fat that the first 25 amino acids are a signal peptide that are not included in the sequence shown. The sequence as shown in SEQ ID NO:2 (which is identical to that shown in Figure 2) begins with numbering at position 1, as required by the MPEP § 2423.03 and 37 C.F.R. § 1.822(d). Claim 66 has been amended to include the sequence (and numbering) as shown in Figure 2, which is also the numbering as referred to throughout the text of the specification" (e.g., see 5/4/07 Response, page 13).

[4] The Examiner agrees and has withdrawn this portion of the rejection.

Accordingly, the New Matter rejection cited above is hereby maintained.

Claims Rejections - 35 U.S.C. § 102

10. Claims 63, 66, 71 and 72 are rejected under 35 U.S.C. 102(b) as being anticipated by Wehrman et al. (Wehrman et al. "Protein-protein interactions monitored in mammalian cells via complementation of β-lactamase enzyme fragments" *PNAS* **March 19, 2002**, *99(6)*, 3469-3474) (3/18/04 IDS, AB).

For ***claim 63***, Wehrman et al. disclose a fragment complementation system (e.g., see Wehrman et al., title wherein a β-lactamase complementation system is disclosed). In addition, Wehrman et al. disclose a first oligopeptide sequence and a second oligopeptide sequence wherein said first oligopeptide sequence is a fusion protein comprised of and in the direction of translation an N-terminal fragment of a Class A β-lactamase protein at least 25 amino acids in length fused through a first break point terminus to a first flexible polypeptide linker and a first interactor domain (e.g., see figure 1A; see also page 3470,

column 2, second to last paragraph wherein the "197 β-lactamase fragment was fused to the amino terminus of the Fos helix [i.e., an interactor domain]"; see also figure 1 showing use of $(Gly_4Ser)_3$ linkers). Wehrman et al. also disclose a said second oligopeptide sequence that is a fusion protein comprised of and in the direction of translation a second interactor domain and a second flexible polypeptide linker fused through a second break point terminus to a C terminal fragment of a class A β-lactamase protein at least 25 amino acids in length (e.g., see figure 1A; see also page 3470, column 2, second to last paragraph wherein the "198 fragment fused to the carboxyl terminus of the Jun helix [i.e., an interactor domain]"; see also figure 1 showing use of $(Gly_4Ser)_3$ linkers). In addition, Wehrman et al. disclose wherein said first and second break point termini within 10 amino acids in either direction from a junction between 2 amino acid residues wherein said 2 amino acid residues are within a solvent exposed loop between elements of secondary structure (e.g., see figure 1 wherein 197/198 junction is disclosed). Finally, Wehrman et al. disclose wherein upon binding of said first interactor domain with said second interactor domain said N-terminal fragment and said C-terminal fragment functionally reconstitute to form the class A β-lactamase protein (e.g., see abstract; see also Results section; see also figures 2-4).

For ***claim 66***, Wehrman et al. disclose fragment complementation wherein said Class A β-lactamase protein comprises SEQ ID NO 2 with the E197/L198 junction (e.g., see figure 1).

For ***claim 71***, Wehrman et al. disclose a fragment complementation system of wherein said first oligopeptide further comprises a first polypeptide linker that separates

the N-terminal fragment of a Class A B-lactamase protein from the first interactor domain wherein said first polypeptide linker is 3-30 amino acids in length and said second oligopeptide further comprises a second polypeptide linker that separates the C-terminal fragment of a Class A B-lactamase protein from the second interactor domain wherein said second polypeptide linker is 3-30 amino acids in length (e.g., see figure 1; see also page 3470, column 2, second to last paragraph wherein the $(Gly_4Ser)_3$ linker is disclosed for each).

For ***claim 72***, Wehrman et al. disclose, for example, HSE, GRE, EKR, and NGR (e.g., see page 3471, column 1, paragraph 1; see also page 3470, column 2, last two paragraphs).

Response

11. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue, "each of the claim elements allegedly disclosed in Wehrman et al. is disclosed at least in eh parent application ... filed on March 15, 2000, which is nearly 2 years prior to the March 19, 2002 publication date of Wehrman et al. Therefore, Wehrman et al. is not prior art" (e.g., see 5/4/07 Response, page 14, especially last two paragraphs).

Applicants have not been afforded priority to the parent application as discussed above and, as a result, Applicants' arguments are moot.

Accordingly, the 35 U.S.C. § 102 rejection cited above is hereby maintained.

Claims Rejections - 35 U.S.C. § 102/103

12. Claims 63, 66, and 71 are rejected under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, 35 U.S.C. § 103(a) as being unpatentable over Michnick et al. (U.S. Patent No. 6,828,099) (Filed May 31, 2001) alone or in view of Galarneau et al. (Galarneau et al., "β-Lactamase protein fragment complementation assays as *in vivo* and *in vitro* sensors of protein-protein interactions" *Nature Biotechnology* **2002**, *20*, 619-622) as further evidenced if necessary by Applicants' Exhibit 1 filed 10/25/06.

For ***claim 63***, Michnick et al. (see entire document) disclose a fragment complementation system (e.g., see Michnick et al., abstract), which anticipates the claimed invention. For example, Michnick et al. disclose a first oligopeptide sequence and a second oligopeptide sequence wherein said first oligopeptide sequence is a fusion protein comprised of and in the direction of translation an N terminal fragment of a Class A β-lactamase protein at least 25 amino acids in length fused through a first break point terminus to a first flexible polypeptide linker and a first interactor domain (e.g., see Example 2 wherein FRB-5a.a.-BLF[1] is disclosed, in this scenario FRB = interactor domain and BLF[1] = 23-197 of TEM-1 β-lactamase fragment and the 5 amino acids represents the linker). In addition, Michnick et al. disclose a second oligopeptide sequence that is a fusion protein comprised of and in the direction of translation a second interactor domain and a second flexible polypeptide linker fused through a second break

point terminus to a C-terminal fragment of a class A β-lactamase protein at least 25 amino acids in length (e.g., see Example 2 wherein FKBP-5a.a.-BLF[2] is disclosed, in this scenario FKBP is the interactor domain and BLF[2] = 198-286 of TEM-1 β-lactamase fragment and the 5 a.a. represents the linker). Michnick et al. do not explicitly disclose the limitation "in the direction of translation" for either fragment, however, both the orientation disclosed in Michnick et al. and the opposite orientation as disclosed by Galarneau et al. (e.g., see figure 2 of Galarneau et al. wherein a 15 amino acid linker was used to connect to two fragments with the claimed orientation instead of two interactor domains) would be immediately envisioned because these are the "only two" orientations that preserve protein folding as exemplified, for example, by Applicants' exhibit 1 (submitted 10/25/06). That is, protein folding is only preserved when a linker or pair of interactor domains bind to the same side of the protein (i.e. see exhibit 1, top figure), not to opposite ends (i.e., see exhibit 1, bottom figure). Therefore, a person of skill in the art would immediately envision both the "insert" and "circular permutation" orientations. *In re Petering* 133 USPQ 275 (CCPA 1962); see also *In re Schauman*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978); see also MPEP § 2131. Alternatively, Michnick et al. inherently disclose this feature in accordance with *In re Graves*, 69 F.3d 1147, 36 USPQ2d 1697 (Fed. Cir. 1995) (prior art reference disclosing a system for testing the integrity of electrical interconnections that did not specifically disclose simultaneous monitoring of output points still anticipated claimed invention if simultaneous monitoring is within the knowledge of a skilled artisan). Here, fusions in the claimed orientation are shown to be within the knowledge of a skilled artisan by Galarneau et al. (e.g., see Galarneau et al.,

figure 2) showing the proper orientation in the QI construct using linker instead of a pair of interactor domains. Furthermore, the term "in the direction of translation" is unclear and, as a result, the metes and bound of the claim cannot be determined (e.g., see 35 U.S.C. § 112, second paragraph below).

In addition, Michnick et al. disclose that said first and second break point termini within 10 amino acids in either direction from a junction between 2 amino acid residues wherein said 2 amino acid residues are within a solvent exposed loop between elements of secondary structure (e.g., see Example 2 wherein the break-point is at positions 197/198, see also column 2, lines 17-33 indicating that positions 196-200 form a solvent exposed loop; see also figure 1). Finally, Michnick et al. disclose binding of said first interactor domain with said second interactor domain said N terminal fragment and said C-terminal fragment functionally reconstitute to form the class A β-lactamase protein (e.g., see figure 4; see also column 3, first full paragraph; see also column 5, lines 43-54).

For ***claim 66***, Michnick et al. also disclose a Class A β-lactamase protein comprises SEQ ID NO 2 (e.g., see Example 2; see also column 1, line 33 disclosing accession number AAB59737). Michnick et al. also disclose said first β-lactamase protein break-point and said second B-lactamase protein break-point are within 10 amino acids in either direction from a junction between 2 amino acid residues in SEQ ID NO 2 selected from the group consisting of P149 and N150 El72 and L173 K190 and V191 A202 and G203 and G228 and K229 (e.g., see Example 2 wherein the 197/198 break-point is dislosed that is within 10 amino acids of K190/V191 or A202/G203).

For ***claim 71***, Michnick et al. also disclose a fragment complementation wherein said first oligopeptide further comprises a first polypeptide linker that separates the N-terminal fragment of a Class A β-lactamase protein from the first interactor domain wherein said first polypeptide linker is 3-30 amino acids in length and said second oligopeptide further comprises a second polypeptide linker that separates the C-terminal fragment of a Class A β-lactamase protein from the second interactor domain wherein said second polypeptide linker is 3-30 amino acids in length (e.g., see Example 2 disclosing the 5 amino acid linker Gly-Gly-Gly-Gly-Ser in each case).

In the alternative that the prior art teachings of Michnick et al. differ from the claimed invention, the difference is set forth as follows:

For ***claim 63***, Michnick et al. fail to teach the a β-lactamase protein covalently bonded "through the C-terminus" of a first class A β-lactamase protein break-point to a first interactor domain and a second oligopeptide comprising a C-terminal fragment of a Class A β-lactamase protein covalently bonded "through the N-terminus" of a second class A β-lactamase protein break-point to a second interactor domain (i.e., this corresponds to the "insert" orientation disclosed in figure 2 of Galarneau et al. wherein a 15 amino acid linker was used to connect to two fragments with the claimed orientation instead of two interactor domains). To the contrary, Michnick et al. disclose just the opposite orientation (i.e., the "circular permutation" orientation, see Galarneau et al., figure 2) wherein a β-lactamase protein is covalently bonded "through the N-terminus" away from the first class A β-lactamase protein break-point to a first interactor domain and a second oligopeptide comprising a C-terminal fragment of a Class A β-lactamase

protein is covalently bonded "through the C-terminus" of a second class A β-lactamase protein away from break-point to a second interactor domain.

However, Galarneau et al. teach the following limitations that are deficient in Michnick et al.:

For ***claim 63***, Galarneau et al. (see entire document) teach the use of rejoining the fragments (albeit with a linker instead of a pair of interactor domains) using the currently claimed orientation (e.g., see figure 2 wherein the QI construct possesses a linker that joins the BLF[1] fragment to he BLF[2] fragment at the 196/198 junction).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to join the interactor domains to the BLF[1] and BLF[2] fragments using their C- and N-termini, respectively (referred to as the "insert" orientation), because Galarneau et al. show that this orientation will not destroy the proper folding and hence activity of the enzyme (e.g., see figure 2, QI construct). Furthermore, a person of ordinary skill in the art would have been motivated to use this orientation instead of the reverse N- and C- termini for BLF[1] and BLF[2], respectively (referred to as the "circular permutation" orientation), because Galarneau et al. disclose that the "insert" orientation retains approximately 40% of the enzymes wild type activity whereas the "circular permutation" orientation retains only about 20% of the enzymes wild type activity (i.e., the "insert" activity is twice as good). Finally, a person of skill in the art would reasonably have expected to be successful because the "insert" orientation does not destroy the proper folding of the enzyme by "reversing" on of the subunits.

Response

13. Applicant's arguments directed to the above 35 U.S.C. § 102/103 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "As discussed above, ... the claims as presently recited claim priority at least to the '106 application filed March 15, 2000, which is 1 year prior to Michnick et al., and two years prior to Galarneau et al. Therefore, the cited references are not prior art" (e.g., see 5/4/07 Response, page 15, paragraph 2).

[1] As discussed above, priority has not been afforded to the '106 application and, as a result, Applicants' arguments are moot.

[2] Applicants argue, "the present invention is not obvious in view of the cited references because the fusions of the interactor domains to the β-lactamase fragments in the claimed orientation as alleged to be shown in Galarneau et al. would not be within the knowledge of a skilled artisan as of the priority date of the present application, because Galarneau et al. was not publicly available as of the priority date of the present application" (e.g., see 5/4/07 Response, page 15, paragraph 3).

[2] Again, priority was not afforded to the '106 application and, as a result, Applicants' arguments are moot.

Accordingly, the 35 U.S.C. § 102/103 rejection cited above is hereby maintained.

New Rejections

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claim 63, 66, and 71-74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. **Claim 63** recites the limitations "the direction of translation" in the newly added amendment (e.g., see line 4). There is insufficient antecedent basis for this limitation in the claim. Correction is requested. Therefore, claim 63 and all dependent claims are rejected under 35 U.S.C. § 112, second paragraph.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
July 18, 2007

JON EPPERSON
PRIMARY EXAMINER